II. REMARKS

Claims 1, 6-8, and 13-15 were examined in the Office Action under reply and stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wierda and O'Brien, *Expert. Rev. Anticancer Ther.* (2001) 1:73-83 ("Wierda"); in view of Dmoszynska et al., *Leuk. Lymphoma* (1999) 34:335-340 ("Dmoszynska"); Denis-Mize et al., *J. Immunother.* (2003) 26:S43 ("Denis-Mize"); and further in view of U.S. Patent No. 4,518,584 to Mark et al. ("Mark"). The Examiner disputes applicants' previous arguments and asserts there would be a reasonable expectation of successful therapy of CLL using the claimed method. However, applicants respectfully disagree with the Examiner's assertions.

As explained in MPEP 2143, the rationale to support a conclusion of obviousness is that all the claimed elements were known in the cited art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP 2143 emphasizes that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966). Additionally, as set forth in MPEP 2142, impermissible hindsight must be avoided and the conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art. Based on these tenets, applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

In particular, Wierda discusses the use of Campath-1H as an immunotherapeutic agent for treating CLL. The Office has acknowledged on the record that Wierda does not teach the combination of aldesleukin and Alemtuzumab, and the administration schemes presented in the dependent claims. See, Office Action dated February 17, 2010, page 4. Additionally, Wierda does not relate to the use of concurrent combination therapy for treating CLL.

Dmoszynska, like Wierda, also does not pertain to the use of concurrent combination therapy for treating CLL, as claimed. Rather, Dmoszynska relates to the use of IL-2 in patients **previously** treated with the chemotherapeutic agent 2 CdA. There is no discussion whatsoever

regarding the use of IL-2 with antibody therapy. Chemotherapeutic agents and antibodies are hardly the same and have completely different mechanisms of action. There is no reason to expect that substituting an antibody such as Alemtuzumab for a chemotherapeutic agent would provide an equivalent response.

Mark, as with the other cited art, also does not pertain to concurrent, combination therapy. In fact Mark does not relate to cancer treatment of any kind, let alone treatment of CLL and merely describes the production of aldesleukin.

As previously pointed out to the Examiner, the only art cited that relates to combining IL-2 therapy with an antibody is Denis-Mize. Denis-Mize does not specify that the patients suffered from CLL and, importantly, Denis-Mize did not use Alemtuzumab but rather Rituximab. These two antibodies are not analogous and therefore cannot be expected to provide analogous responses. The antibodies are directed against different surface antigens and therefore bind to different ligands. The two antibodies are unrelated and the efficacy of substituting one antibody for the other is not predictable.

The Examiner disputes this argument, stating: "One would have a reasonable expectation of a successful therapy of CLL using the method of the cited combined art, in view that a combination of IL-2 with an anticancer drug or antibody has been shown to be successful for treating cancer, in view of the teaching of Dmoszynska et al. and Denis-Mize et al, of record." However, this argument completely ignores the fact that none of the cited art teaches concurrent therapy as claimed and, importantly, a chemotherapeutic agent, such as described in Dmoszynska and the antibody described in Denis-Mize are simply not analogous, either structurally or functionally, to Alemtuzumab. There would be no reason to expect that the use of a completely different molecule in combination with IL-2 using a different treatment regimen would elicit the same results.

Furthermore, the Examiner continues to assert that applicants merely determined "optimum concentration of reactants." However, as previous explained, the claimed method is not merely "optimization" that one of skill in the art achieved through "routine experimentation." The skilled artisan simply could not predict that a treatment regimen as claimed would indeed be efficacious. Cancer therapy is extremely complex and it is well known that the timing of

administration is critical.

Additionally, the Office disputes applicants' arguments regarding the possibility of drug-drug interactions in combination therapy that can result, *inter alia*, in a non-existent or diminished effect of one or both of the agents, or the appearance of new effects not seen with either drug alone. Applicants previously submitted Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Publishing Division, 2001, pages 54-56 which clearly supports the proposition that the efficacy of two agents in combination, such as aldesleukin and Alemtuzumab, is unpredictable. The Examiner has provided no evidence to the contrary

The Office states applicants have not "provided any reference showing a severe toxicity due to the particular interaction between IL-2 and the anti-CD52 antibody taught by the combined art." However, such art is not possible to provide as there does not appear to be prior art directed to the use of applicants' claimed method.

Applicants continue to assert the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions" (*KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007)) Rather, as explained above, the evidence is to the contrary.

Additionally, it is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and a rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

III. CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and request early notification to that effect. The Examiner is encouraged to contact the undersigned if the Examiner notes any further matters which might be resolved by a telephone interview.

Respectfully submitted,

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By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: 650-493-3400
Facsimile: 650-493-3440